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Physics-based Models of Brain Structure Connectivity Informed by Diffusion-weighted Imaging

by Jean M Vettel, Ph.D., Danielle Bassett, Ph.D., Reuben Kraft, Ph.D., and Scott Grafton, M.D.

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Army Research Laboratory
Aberdeen Proving Ground, MD 21005

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14. ABSTRACT

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PHYSICS-BASED MODELS OF BRAIN STRUCTURE CONNECTIVITY INFORMED BY DIFFUSION-WEIGHTED IMAGING

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ABSTRACT

Recent evidence indicates that neural adaptations related to changes in task performance occur in not only gray matter brain regions but also the white matter fiber tracts that connect the gray matter regions with one another. Here, we propose a framework for linking individual differences in global properties of the brain's anatomical connectivity, or connectome, to individual differences in task performance. We argue that this analysis framework may be optimally used on groups of patients with particular cognitive impairments to increase the dynamic range of task performance and optimize our sensitivity to detect structure-function relationships. In particular, patients suffering from mild traumatic brain injury may be an ideal group based on evidence suggesting an underlying cause of diffuse axonal injury that is widespread throughout the brain yet not detectable on structural magnetic resonance imaging (MRI) or computer tomography (CT) brain scans. The data discussed here lays the foundation for research on individual differences in structure-function relationships by comparing two diffusion-weighted imaging techniques that can be used to examine white matter structure *in vivo* in order to determine if one technique provides more reliable estimates of structural variability between individuals. While both methods show reproducibility of a particular individual's brain structure, Diffusion Tensor Imaging appears better able to reliably capture the variability between subjects. We conclude with a description of a physics-based modeling approach using diffusion-weighted imaging data that facilitates several avenues of Army-relevant research.

1. INTRODUCTION

Every Soldier masters a set of skills essential for their missions and develops operationally relevant expertise in particular task domains. As expected, these differences in experience lead to differences in performance on various cognitive tasks based on experience-dependent plasticity in the brain. Classically, these changes were thought to occur in the gray matter regions of the cortex, but recently, research has suggested that neural adaptations can be seen in the white matter fiber tracts as well **(**Bosnell et al., 2008**).**

White matter fiber tracts contain bundles of neuronal axons that connect different gray matter regions of the brain with one another, with approximately 10^{15} fiber tract pathways collectively providing the anatomical substrate for the brain's efficient information processing. Changes in fiber tract connections have been found over a range of temporal scales. In school-age children, changes in white matter are correlated with language ability, working memory capacity, and measures of IQ (Cascio et al., 2007). Research on professional concert pianists in their thirties found that differences in fiber tract organization reflected the number of practicing hours during adolescence (Bengtsson et al., 2005). Studies of aging reveal changes in white matter that can predict speed of reaction time on a visual target detection task (Madden et al, 2004). Interestingly, over a much shorter time frame of only 6 weeks, a reconfiguration of fiber tract organization was measured in adults after the acquisition of a newly acquired motor skill, juggling (Scholz et al., 2009). Converging evidence from across the lifespan, and at varying time scales, indicates that differences in white

matter fiber tract connections between individuals correlate with differences in task performance.

In this paper, we discuss a proposed framework for investigating the relationships between brain structure and cognitive function using a cognitively impaired population. Comparing patients to healthy controls increases the dynamic range of performance and optimizes our sensitivity to detect differences in structural connectivity that can be correlated with differences in task performance. Due to its prevalence among both military and civilian populations, mild traumatic brain injury (mTBI) is described as a potential test case to examine the efficacy of this approach based upon recent evidence suggesting that diffuse axonal injury may underlie mTBI symptoms (Smith et al., 2003). Diffuse axonal injury is characterized by widespread degradation of the axonal fibers throughout the brain, yet existing research has only explored a region-based analysis approach to identify correlations between structural damage and cognitive impairments (Kraus et al., 2007; Kumar et al., 2008; Rutgers et al., 2008; Wang et al., 2008; Xu et al., 2007). Here, we suggest that detection of these structural changes may be more accurately identified using complex network theory, which provides a set of analysis tools to characterize the global properties of brain connectivity, thereby enhancing the existing research that relies on smaller, segregated brain regions of interest. Complex network theory has recently emerged as an important analytic approach for the understanding of the brain's structural connectivity, or connectome, and brain function (Bullmore & Sporns, 2009).

This proposed analysis framework depends on *in vivo* imaging of brain structure in order to reconstruct an individual's structural connectome. In this study, we compare two brain imaging techniques, the traditional Diffusion Tensor Imaging (DTI) method and the recently proposed method, Diffusion Spectrum Imaging (DSI). Both are diffusion-weighted imaging techniques that use the directionality of water movement in the brain to estimate the location and orientation of white matter fiber tracts, but they differ in the number of orientations that they image of the brain. The goal of the study was to identify which technique most reliably captured the structural variability between individual subjects across different scanning sessions. Using both a region of interest and a connectome-based approach, we found that both imaging techniques showed relatively stable estimates of an individual's structural connectome, but diffusion tensor imaging provided a more reliable structural description to discriminate between subjects across imaging sessions over time, a feature essential for the study of individual differences. Finally, we conclude with a discussion of future directions to use diffusion tensor imaging to develop a physics-based model of structural connectivity for the brain and describe several avenues of research that can be supported by this modeling effort.

2. MILD TRAUMATIC BRAIN INJURY

Traumatic Brain Injury (TBI) occurs when an external force impacts the head and causes a loss of consciousness, amnesia, and/or alterations in normal brain function. In the last 10 years, almost 180,000 military personnel have been clinically confirmed as TBI cases according to the medical records collected by the Defense and Veterans Brain Injury Center (http://www.health.mil/Research/TBI_Numbers.aspx). The Congressional Brain Injury Task Force suggests that TBI is underreported, and their estimates suggest that 360,000 military personnel have been inflicted by TBI throughout the wars in Iraq and Afghanistan (http://pascrell.house.gov/work/braininjury.shtml). In addition to these military incidents, a report from the Centers for Disease Control and Prevention (CDC) estimates that 1.7 million civilians suffer a TBI each year (Faul et. al., 2010). Collectively, almost 2 million Americans suffer from TBI-induced symptoms each year.

TBI is classified based on severity (severe, moderate, mild) and mechanism (closed or penetrating head injury), and this paper will describe the largest subpopulation of TBI injuries – mild TBI (mTBI) in closed head injury cases. Within military settings, approximately 99% of all casualties between October 2001 and July 2010 were based on blast or impact injury (http://siadapp.dmdc.osd.mil/personnel/CASUALTY/castop.htm). Within civilian settings, approximately 79% of all mTBI injuries between 2002 and 2006 involved similar mechanisms (Faul et. al., 2010). A substantial variety of cognitive impairments exists within this large population of mTBI patients. According to the guidelines set forth in a Memo from S. Ward Casscells on October 1, 2007, the definition of mTBI includes four criteria: normal structural imaging based on MRI and CT, a loss of consciousness between 0 and 30 minutes directly following the TBI incident, an alteration of consciousness that can last up to a day, and short-lived post-traumatic amnesia directly following the insult. Within this loose range of diagnostic criteria, the variations of the mTBI incident are substantial, and consequently, the nature of the cognitive impairments is also incredibly diverse. Thus, there is a significant need to identify a neuroimaging technique sensitive enough to reveal these variations in neural damage in order to enable research to differentiate the underlying causes for the large number of patients diagnosed with different manifestations of mTBI.

Our research interest is not in the clinical aspects of mTBI; instead, our interest arises based on the large subgroups of mTBI patients who present with similar

cognitive impairments. These patients provide a promising avenue for understanding relationships between structural differences that correlate with differences in task performance. Comparing mTBI patients to age-matched, healthy controls will increase the range of performance on particular cognitive tasks, and thus, the comparison increases our sensitivity to detect links between brain structure and cognitive function. Our interest in this particular patient population is augmented by the recent evidence suggesting that diffuse axonal injury may underlie at least some variants of mTBI, a type of structural variation between individuals that may be particularly amenable to a complex network analysis framework.

3. DIFFUSE AXONAL INJURY

Diffuse axonal injury (DAI) is characterized by widespread lesions in white matter fiber tracts and results from traumatic shearing forces typically caused in both blast and impact injuries (Taber et al., 2008). Both of these injuries can cause a complex pattern of acceleration and deceleration of cortical and subcortical structures in the brain. Basic physics defines acceleration as the rate of change in velocity over time, where velocity depends on both mass of the object and force acting on the object. Based on the variability of their density, or mass per unit volume, the cortical and subcortical structures have very different momentum at the time of impact. The consequent heterogeneity of momentum across the brain can cause significant shearing and deformation effects. In fact, it is the large density differences in the deep and subcortical white matter, especially corpus callosum and brainstem, that makes these brain regions particularly vulnerable to impact (Smith et al., 2003). In severe TBI, these shearing and deformation forces can immediately injure axons (Le and Gean, 2009); however, these forces may also trigger a cascade of biochemical and cellular mechanisms which can degrade neuronal cell bodies and complex neural networks over the course of hours, days, and even months (Smith et al., 2003). The slow, evolving nature of these cascades is thought to manifest through large- and multi-scale network deficiency, causing altered function of networks within networks.

A patient with DAI usually presents with several cognitive impairments but completely normal diagnostic magnetic resonance imaging (MRI) and computer tomography (CT) scans. Consequently, DAI has been referred to as a "diagnosis of exclusion" (Smith et al., 2003) since a definite diagnosis is only possible on autopsy (Kumar et al., 2008) when examination of postmortem histological slices uncovers systemic abnormalities in axonal structure (Taber et al., 2008). In the last ten years, however, several studies have suggested that a recent neuroimaging technique known as diffusion weighting imaging holds promise for visualizing the more intricate details of white matter fiber tracts in the brain. It is therefore intuitively plausible that diffusion imaging may offer an *in vivo* imaging method to quantify DAI damage (Le and Gean, 2009; Smith et al., 2003; Xu et al., 2007).

4. DIFFUSION-WEIGHTED IMAGING

Images of a person's white matter fiber tracts can be obtained using an MRI scanner with a technique known as diffusion-weighted imaging. This imaging technique measures the direction that water is moving in different regions of the brain, and this directional movement reveals the local brain structure since water diffuses in the same direction as the local fiber tract. To estimate the direction of water movement, this technique divides the entire brain into smaller cubes called voxels, which are similar to the pixels of a picture image, and records whether any water is moving within that small, 1-5mm voxel. The estimated strength of the water diffusion within each voxel is interpreted as a measure of the structural integrity of the fiber tracts in that brain region. The most common measure for voxel-by-voxel estimates of white matter integrity is Fractional Anisotropy (FA). In addition, complete fiber tracts can be reconstructed from these voxel estimates of diffusion by integrating data from nearby cubes to identify the direction of the tract. The output of this reconstruction procedure, known as tractography, produces a whole brain image of a person's fiber tract structure (see Figure 1 for an example). Using either FA values or metrics about fiber tracts, current research has investigated whether anatomically defined regions of interest, containing a few hundred voxels, can distinguish TBI patients from healthy controls.

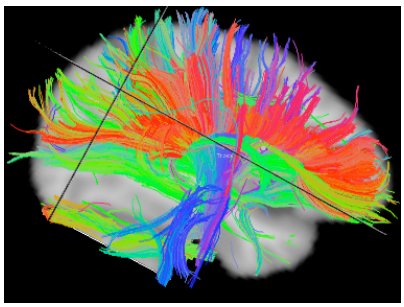

Fig. 1 An example of reconstructed tractography for a study participant that passes through a particular medial brain region. Fiber tracts are overlaid on the participant's anatomical brain scan.

Region-based approaches using diffusion-weighted imaging have found correlations between white matter microstructure and neuropsychological measures of

cognitive performance (Kraus et al., 2007; Kumar et al., 2008) as well as tractography measures of fiber tract integrity (Rutgers et al., 2008; Wang et al., 2008; Xu et al., 2007). However, all but one of these studies used a mixed sample of both mild and moderate-to-severe TBI patients, increasing the expected level of structural damage in the patient group and therefore increasing the ability to detect it. In addition, the studies investigated only a small subset of regions (minimum of 5, maximum of 14), focusing on the medial regions near the corpus callosum that are frequently identified as damaged in severe TBI injuries (Smith et al., 2003). The exception is the study by Rutgers and colleagues (2008) that compared *only mTBI* patients to controls, using a whole-brain analysis to identify brain areas with reduced FA scores in patients. On average, each patient had 9 brain regions with reduced FA, and these regions varied among individuals (perhaps due to different cognitive impairments; no neuropsychological tests were performed). Interestingly, the authors emphasize that the regions identified for these mTBI patients are not the ones identified in severe TBI (and used in the majority of the other region of interest studies). Overall, these studies highlight the promise of diffusion-weighted imaging to elucidate and quantify the structural damage underlying DAI. While the region-based approach has proven useful, the probable mechanisms of DAI strongly underscore the possibility of extensive individual variability across the entire brain, as suggested by Rutgers and colleagues (2008). We propose that network analysis methods which are more sensitive to large-scale changes in connectivity patterns may enhance the sensitivity to structural changes underlying the cognitive impairments of mTBI patients.

5. COMPLEX NETWORK ANALYSIS: STRUCTURAL CONNECTOME

Complex network theory provides a mathematical and physics-based modeling framework in which to understand the large-scale connectivity architecture of complex systems like the human brain (Albert & Barabasi, 2002). In the neuroimaging community, complex network analysis is a swiftly growing field of neuroscientific investigation (Bullmore & Sporns, 2009), particularly in the characterization of the large-scale organization of white matter connectivity (Hagmann et al., 2008) as measured by diffusion-weighted imaging (Moseley et al., 1990). Importantly, recent work has shown that complex network models of diffusion tractography are highly sensitive to individual variation and reproducible over multiple scanning sessions (Bassett et al., 2010).

Complex network models of the brain are constructed by first defining the sub-parts of the system (in this case brain regions, also termed 'vertices' V in complex network theory) and the relationships between those sub-parts (in this case white matter tracts, also termed 'edges', E) (Bullmore & Bassett, 2010). Together, the vertices and edges form a graph, G, which can be represented by a VxV adjacency matrix, A, whose ij^{th} element indicates whether vertex i is connected to vertex j ($A_{ij}>0$) or not ($A_{ij}=0$). A complex network model of white matter architecture would therefore have $A_{ij}>0$ if brain region i was connected by a white matter tract to brain region j and $A_{ij}=0$ otherwise. Such a model of the complete architecture of anatomical connectivity has been dubbed the `connectome' (Sporns et al., 2005), and it can be studied using a wealth of currently available graph metrics (Rubinov & Sporns, 2009). An example of a structural connectome is shown in Figure 2. Recent work has suggested that connectome architecture is modulated by healthy variability in age and sex (Gong et al., 2009), but also by disease (Bassett et al., 2008; He et al., 2009).

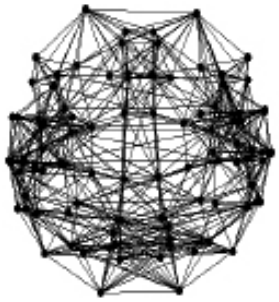

Fig. 2 An example of a structural connectome where brain regions are represented by vertices (black circles) and white matter tracts as edges (black lines).

However, while multiple diagnostics of network architecture have been proposed (Bassett & Bullmore, 2009), none have been tested for sensitivity in the context of diffuse brain injury. Focal brain injuries in specific brain regions, on the other hand, have been studied, usually in the context of stroke (De Vico Fallani et al., 2009; Wang et al., 2010). In recent work, Crofts and colleagues (2009) provide initial evidence for the usefulness of a diagnostic of network architecture known as communicability in the context of focal injury that may be a viable diagnostic for diffuse axonal injury as well.

Communicability is intuitively a measure of the ease of information transfer within the system (Estrada et al., 2008). Many metrics available in the graph theory literature are related to the length of the path between any two nodes i and j, which is defined as the number of connections that need to be traversed on the graph in order to move from node i to node j. The communicability, however, is based on the concept of a walk rather than a path, where the number of walks of length k between node i and j is given by the k^{th} power of

the adjacency matrix, A: $(A^k)_{ij}$. Using this observation, and including a correction for the increased likelihood of information passing over short walks rather than over long walks, Crofts and Higham (2009) provide a measure of theoretical ease of biologically relevant information flow from any region of the cortex to any other region over the complex pattern of white matter tracts in a single individual's brain.

In a follow up study, Crofts and colleagues (2010) show that the communicability of cortical networks can be used to fully separate stroke patients, who had lesions in left hemisphere subcortical structures, from healthy controls. Importantly, the subjects could be correctly categorized not only by modeling the connectivity of the lesioned hemisphere but also that of the unaffected hemisphere. These results suggest two important consequences: 1) changes in white matter structure can occur in areas far removed from the affected site, and 2) the complex network measure of communicability can be used to detect these diffuse changes in white matter microstructure.

In summary, given the sensitivity of communicability to detect axonal changes as a consequence stroke (Crofts and Higham 2009; Crofts et al., 2010), we propose to examine the communicability of white matter connectivity measured via diffusion-weighted imaging on a population of mTBI patients in order to determine whether diffuse changes in white matter microstructure can be linked to cognitive decrements in this population. We hypothesize that we may be able to gain additional power over previous region of interest-based studies by leveraging the connectome-based approach due to its theoretically heightened sensitivity to whole brain patterns. Within the connectome framework, communicability may provide the most direct and appropriate measure to detect both diffuse and systemic white matter injury, although a variety of other graph metrics may also prove useful.

6. INDIVIDUAL DIFFERENCES IN STRUCTURE

Before embarking on our effort to investigate the relationship between individual differences in structural connectivity and differences in task performance, we must evaluate which diffusion-weighted imaging technique reliably captures the structural variability between individual subjects over time. In other words, which technique can reliably discriminate among individuals.

One of the critical parameters for a diffusion-weighted MRI scan is the number of diffusion directions that can be measured in the brain. Classically, an MRI scan images a few millimeters at a time from bottom to top, left to right, or front to back. In a diffusion-weighted MRI scan, however, the brain images are taken at many different angles in order to better obtain an estimate of water diffusion since the fiber tracts can cause the water to flow through any angle. Currently, there are two techniques for diffusion-weighted imaging, and they differ based on the number of orientations they measure. The traditional method, Diffusion Tensor Imaging (DTI), typically measures 30-60 orientations, while a newer, more recently proposed method, Diffusion Spectrum Imaging (DSI), typically measures 124-514 orientations.

For this study, we collected a total of six diffusion-weighted images for each individual (N=6) across six different scanning sessions. Three of the images were collected using DTI and three using DSI. This design facilitated an analysis of the within-subject reproducibility (comparing sessions 1, 2, and 3 of the same participant) as well as an analysis of between-subject variability (comparing sessions 1, 2, and 3 of participant A with sessions 1, 2, and 3 of the other five participants, B-F). In addition, we can compare these variability measures between techniques since we have triplicate sessions for every participant for both DTI and DSI. In particular, we are interested in whether we find an interaction in this 2x2 design (within/between variability & DTI/DSI technique) which would indicate that one technique provides better discrimination between individuals. The interaction would indicate that one technique is more sensitive to individual differences in fiber tract structure.

In order to examine differences between the techniques, we conducted an analysis on the tractography for each participant. For this analysis, we used the Johns Hopkins atlas of white matter regions to conduct a region of interest analysis that investigated the reliability of the number of tracts estimated within each region across the scanning sessions.

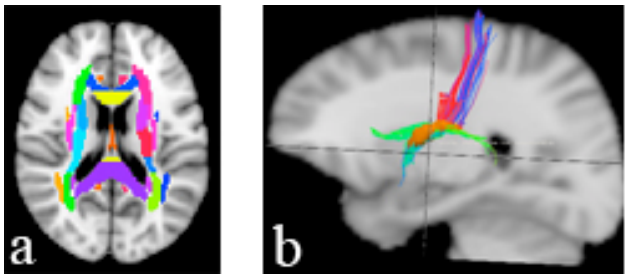

Fig. 3 A subset of the JHU White Matter Atlas regions are shown in different colors (a), and the tracts (in various colors) that pass through one of the regions (shown in orange) for an example participant.

The within- and between-subjects variability was computed for every participant (n=6) and every white matter atlas region (n=48) for both diffusion-weighted

imaging techniques (n=2). We then collapsed over the six participants and the forty-eight regions to run a 2x2 ANOVA of variability type (within vs between subjects) and imaging technique type (DTI vs DSI). We found a main effect of variability type ($p<0.0010$), indicating that both diffusion imaging techniques have less variability within participant than between participants. This result indicates that, as expected, the brain structure of any single individual participants was more similar to other scans from the same individual than to scans from other individuals. Importantly, the ANOVA also showed a significant interaction ($p<0.0021$), indicating that the DTI method had a greater difference across the within-subjects variability and between-subjects variability than the DSI method. This suggests that the DTI technique can measure individual differences better than DSI. The 2x2 ANOVA results are shown in Figure 4.

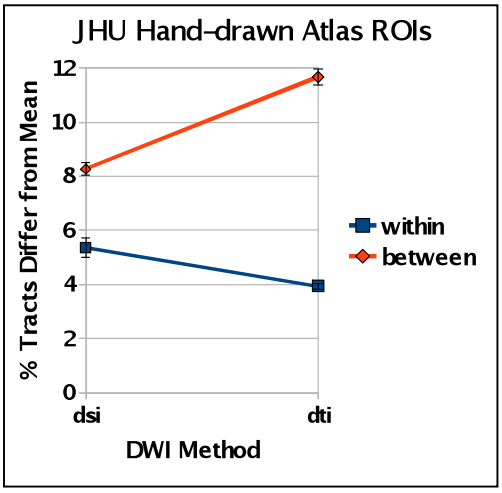

Fig. 4 This plot shows the average number of tracts that were reproducible, collapsed across 48 regions of interest from the JHU White Matter Atlas. If the number of tracts were perfectly reproducible between scanning sessions, the percentage from tracts that differ from the mean would be zero. A 2x2 ANOVA showing a main effect of variability ($p<0.0010$), showing the expected result that a given participant was more similar to themselves than to another participant, and an interaction ($p<0.0021$), indicating greater separation of within- and between-subject variability for DTI.

Importantly, the same pattern of results was found on this same dataset using a connectome-based analysis approach to compare reproducibility of the two techniques (Bassett et al., 2010). Both the region of interest and connectome analyses provide converging evidence that the DTI imaging technique can discriminate individuals more reliably than the DSI technique. In addition, these results show good correspondence between a region-based approach and a connectome-based approach, suggesting that our proposed connectome-framework can enhance the existing research that uses mTBI patients to investigate individual differences in structure that can be linked to differences in cognitive function.

7. FINITE ELEMENT MODEL

To complement this proposed framework to investigate structure-function relationships in mTBI populations, we will construct computationally-based tools to model the physics of structural damage. The benefits of this modeling are three-fold: (1) the ability to understand the process of structural brain mechanics and physics from the insult to the injury; (2) the ability to examine the sensitivity of analysis metrics to detect well characterized damage; and (3) the development of a robust computational design platform for Warfighter protection.

The finite element method provides a tool to simulate the complex blast environment, including the explosive gas dynamics, the blast wave propagation, and the resulting blast-induced loading to the human head. Figure 5a-d shows various views of the human body finite element model currently being used at the ARL both to assess injury and to design Warfighter protection (Kraft and Ziegler, 2010). Currently, within the model, brain tissue is represented as an isotropic, hyperviscoelastic material, which ignores microstructural detail, such as axonal fiber tracts.

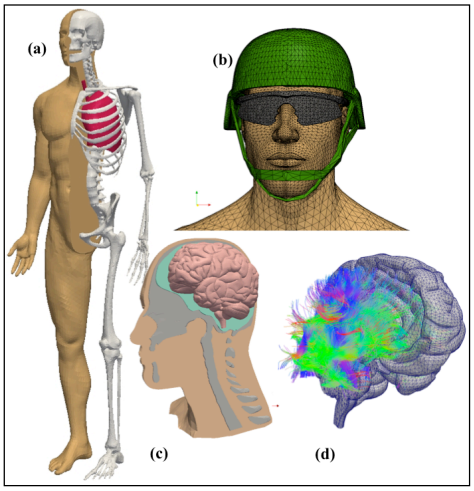

Fig. 5 Various views of the ARL human body finite element model. (a) full body model, (b) mesh view of sub-model of head with Advanced Combat Helmet and Sawfly® standard issue eye protection, (c) cut-away view of internal mesh structure, and (d) schematic of DTI tractography superimposed on brain volume mesh.

As discussed earlier, DTI offers details about the underlying microstructure of brain white matter that can be incorporated into the finite element model using transversely isotropic constitutive laws. This process includes building finite element models of the human brain based on high-resolution MRI scans for the geometry and the corresponding DTI information to inform an element level constitutive model. In other words, each finite element that represents a continuum of brain tissue is assigned an axonal fiber orientation obtained from DTI tractography. A schematic representation of this is shown in Figure 5d. Including the microstructural level of detail will provide a degree of mechanical rigidity that will constrain the directional propagation of shock waves throughout the brain. This model can then be used to simulate how blast forces propagate through the brain and interact with the underlying white matter microstructure, possibly inducing diffuse axonal injury.

Based on the model simulations, we can then examine the sensitivity of both region-based and connectome-based metrics of structural integrity where the "ground-truth" is known about the structural damage. For example, these simulated datasets could reveal how much structural damage must be present to be identified by either analysis metric. The datasets could reveal whether the level of detectable damage varies across different brain regions. The model provides a test bed for evaluating the sensitivity and reliability of analysis methods.

In the long-term, this finite element model may enable a tighter link between the type of blast and the resulting structural damage in individual soldiers. This link would facilitate the design of more optimal protection. These designs could be further enhanced if the structural damage can be linked with task performance decrements, indicating regions of the brain that are the least resistant to a TBI insult.

CONCLUSION

This paper proposed a novel analysis framework to investigate structure-function relationships by comparing patients with similar cognitive impairments to matched, healthy controls. We propose groups of mTBI patients to be a viable test case population based on the prevalence of the injury across both military and civilian individuals as well as research suggesting that diffuse axonal injury may be an underlying cause. Recent research indicates that diffusion-weighted imaging may be able to capture the widespread structural damage *in vivo* that is indicative of diffuse axonal injury in post-mortem studies. Here, we compared the ability of two diffusion-weighted imaging techniques, Diffusion Tensor Imaging and Diffusion Spectrum Imaging, to investigate if one technique was able to better discriminate the structural differences between individuals across scanning sessions. We found that both imaging techniques showed relatively stable estimates of an individual's structural connectome, but Diffusion Tensor Imaging provided a more reliable structural description to discriminate between subjects across imaging sessions over time, a feature essential for the study of individual differences. We intend to incorporate a structural connectome into the existing finite element Digital Warrior head model to increase the fidelity of the model; importantly, this modeling effort also provides an avenue to simulate how blast force propagation links to structural damage. These simulated datasets of damage can be used to assess the sensitivity of analysis metrics as well as eventually inform designs to protect Soldiers in theater.

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